REMARKS

1. Status of claims

After entry of the above amendment, claims 1-10, 24-29, and 32-48 are pending and under consideration.

2. Support for amendment

The amendment of claim 24 finds support p. 13, lines 8-11, and claim 1 as previously amended. The amendment of claims 35 and 41 corrects a typographical error. No new matter has been added by the amendments.

3. Claim rejections under 35 U.S.C. §103

First, the Examiner rejected claims 1, 3-5, 8, 10, 24-27, and 32-48 under 35 U.S.C. §103(a) as being unpatentable over Ohura *et al.*, *J. Biomed. Mat. Res.* (1999), 44(2), 168-175 ("Ohura") in view of Chen *et al.*, US 5,707,962 ("Chen"). Applicant respectfully traverses this rejection.

The Examiner pointed to Ohura as teaching a cement comprising tricalcium phosphate (TCP), monocalcium phosphate monohydrate (MCPM), and bone morphogenetic protein (BMP)-2, and to Chen as teaching collagen matrices in bone formation compositions.

The present claims recite compositions that, among other elements, have acidic pHs capable of enhancing bone growth protein induced bone formation.

Neither Ohura nor Chen teaches or suggests acidic pHs that are capable of enhancing bone growth protein induced bone formation. First, Ohura pointed to other work in which BMP

and basic TCP produced 12-fold more bone than BMP alone (p. 168, col. 1), which indicates basic TCP is bioavailable when implanted into a mammal. Second, Ohura teaches a composition in which basic TCP is present at about 6 times the weight of MCPM. Although TCP is far less soluble than MCPM, the skilled artisan would recognize that in the mixture of Ohura, a reaction between TCP and MCPM would take place that would produce calcium hydrogen phosphate. The calcium hydrogen phosphate would raise the pH, to pH 7.0 after about 1 hr and eventually to an equilibrium pH 7.2 after 24 hr. Ohura teaches the TCP/MCPM mixture sat at 180°C for 1 hr and was thereafter refrigerated until use, suggesting Ohura's compositions are neutral or basic when implanted in the animal (p. 169, col. 1). Therefore, Applicant disagrees with the Examiner's allegation that TCP would not contribute to the pH of the composition of Ohura and Ohura's composition would have an acidic pH. Chen is silent regarding which if any pH is preferred.

Further, neither Ohura nor Chen teach or suggest that certain acidic pHs can be capable of enhancing bone growth protein induced bone formation. The references do not discuss the activity of any bone growth proteins as a function of pH. Ohura, in fact, teaches away from acidic pHs by pointing to other work in which BMP and basic TCP produced 12-fold more bone than BMP alone (p. 168, col. 1). Because the references provide no teaching or suggestion that certain acidic pHs can be capable of enhancing bone growth protein induced bone formation, they cannot render obvious present claims 1, 3-5, 8, 10, 24-27, and 32-48.

Second, the Examiner rejected claims 1-8, 10, and 28-29 under 35 U.S.C. §103(a) as being unpatentable over Kwan *et al.*, US 6,187,047 ("Kwan") in view of Constantz, US 5,047,031 ("Constantz"). Applicant respectfully traverses this rejection.

The Examiner pointed to Kwan as teaching compositions comprising collagen substrates, calcium phosphates, and bone growth proteins, but being silent concerning acidic calcium phosphates. The Examiner pointed to Constantz as teaching acidic calcium phosphates.

As stated, the present claims recite compositions that, among other elements, have acidic pHs capable of enhancing bone growth protein induced bone formation.

Although Constantz teaches acidic calcium phosphates, there is no motivation to combine Constantz and Kwan because Constantz is silent regarding the impact of acidic pH on bone growth protein induced bone formation. Moreover, Constantz provides no evidence that acidic pHs could enhance bone growth protein induced bone formation. Applicant, in contrast to this art and the expectation of the ordinary skilled artisan in the absence of the present disclosure, provides extensive evidence that acidic pHs can enhance bone growth protein induced bone formation (Figures 2-6). Applicant strongly disagrees with the Examiner's contention that Applicant's evidence shows merely a linear effect of acidic calcium phosphates in combination with bone growth proteins, relative to either class of compounds alone. Applicant submits that acidic calcium phosphates have an unexpected synergistic effect on the activity of bone growth proteins. Several points support this submission.

First, as Applicant has stated, the skilled artisan as of the date of the present invention would have considered acidic calcium phosphates to be inferior, or at best equivalent, to basic calcium phosphates in bone repair applications. Thus, one of ordinary skill in the art beginning with the art-supported presupposition that the acidity of a calcium phosphate has either a negative or negligible impact on bone repair would necessarily find the superior explant masses and histology scores shown in Figs. 2-3 and 6-7 for acidic calcium phosphates/bone growth proteins versus basic calcium phosphates/bone growth proteins to be surprising and unexpected.

Stated another way, to the surprise of the inventor and others skilled in the art, the acidic calcium phosphates not only failed to diminish bone growth protein activity, nor merely maintain unchanged bone growth protein activity, but they were clearly and convincingly shown to stimulate bone growth protein activity above that shown for basic calcium phosphates, the prior state of the art.

Also, Figures 4-5 indicate little difference in mineral concentration for compositions comprising acidic calcium phosphates/bone growth proteins or basic calcium phosphates/bone growth proteins. This suggests that both acidic and basic sources of calcium phosphate can stimulate bone growth of a normal physiological composition. Moreover, this also suggests that the superior explant masses and histology scores for acidic calcium phosphates/bone growth proteins (*i.e.*, indicators of bone growth quantity and quality) represent an unexpected synergistic effect between acidic calcium phosphates and bone growth proteins. This synergistic effect does not flow naturally from the suggestions of the prior art. Constantz and Kwan do not guide the skilled artisan to this synergistic effect.

Therefore, neither Constantz nor Kwan, alone or in combination, teaches or suggests compositions featuring acidic pHs *capable of enhancing bone growth protein induced bone formation.* Applicant respectfully requests this rejection of claims 1-8, 10, and 28-29 be withdrawn.

4. Conclusion

Applicant submits all pending claims under consideration, 1-10, 24-29, and 32-48, are in condition for allowance. The Examiner is invited to contact the undersigned patent agent at (713) 934-4065 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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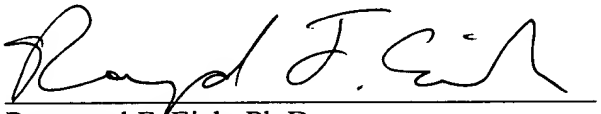

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